

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/135	A1	(11) International Publication Number: WO 97/17067 (43) International Publication Date: 15 May 1997 (15.05.97)
(21) International Application Number: PCT/US96/17745 (22) International Filing Date: 5 November 1996 (05.11.96) (30) Priority Data: 60/007,325 6 November 1995 (06.11.95) US (71) Applicant (for all designated States except US): SOMERSET PHARMACEUTICALS, INC. [US/US]; 5415 West Laurel Street, Tampa, FL 33607-1729 (US). (72) Inventor; and (75) Inventor/Applicant (for US only): DiSANTO, Anthony, R. [US/US]; 18305 Parrish Grove Road, Dade City, FL 33525 (US). (74) Agent: SANZO, Michael, A.; Vinson & Elkins, 1455 Pennsylvania Avenue N.W., Washington, DC 20004-1008 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: SUBLINGUAL AND BUCCAL ADMINISTRATION OF SELEGILINE		
(57) Abstract <p>The present invention is directed to improved methods for treating certain selegiline-responsive diseases or conditions and, more specifically, to methods in which selegiline is administered buccally or sublingually. Selegiline may be used either as a free base or as a pharmaceutically acceptable acid addition salt. The selegiline-responsive diseases or conditions include neuronal-degenerative diseases and conditions, such as Alzheimer's disease and neuronal damage from hypoxia, stroke, ischemia, and trauma, and dopaminergic-related, selegiline responsive diseases and conditions such as depression and ADHD.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

SUBLINGUAL AND BUCCAL ADMINISTRATION OF SELEGILINE

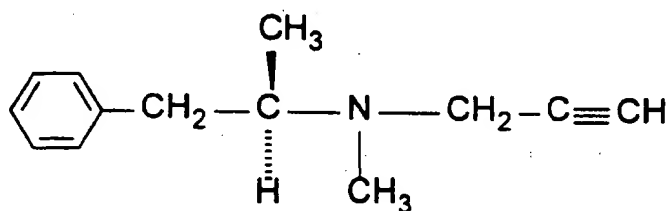
Field of the Invention

5 The present invention pertains to improved methods for using selegiline in therapeutic applications. In particular, the invention is directed to improved methods for treating certain selegiline-responsive diseases and conditions by administering selegiline either buccally or sublingually.

Background of the Invention

10 Selegiline, including its acid addition salt forms, has heretofore been known to be useful for veterinary and clinical purposes because of its neuronal-protective or neuronal-regenerative effects and its dopaminergic effects, i.e., its selective inhibition of the enzymatic degradation of dopamine by monoamine oxidase B. Selegiline, i.e., R-(-)-N-methyl-N-(prop-2-ynyl)-2-aminophenylpropane, also known as L-(-)-deprenyl or R-(-)-deprenyl, has the following structural formula:

15



20 The discovery of selegiline initially represented an important therapeutic improvement over known non-selective monoamine oxidase inhibitors, e.g., tranlylcypromine. Tranlylcypromine was introduced more than thirty years ago for the treatment of depression, but was subsequently withdrawn from clinical use because of a severe hypertensive side effect, the so-called "cheese effect". Tranlylcypromine was non-selective with respect to the two distinct monoamine oxidase enzymes: monoamine oxidase A (MAO-A) and monoamine oxidase B (MAO-B). In particular, the cDNAs encoding these enzymes show different promoter regions and distinct exon portions, indicating they are encoded independently at different gene positions, and analysis of the two proteins has shown differences in their respective amino acid sequences.

25

The relative selectivity of selegiline in the inhibition of MAO-B is important to its safety profile following oral administration. The "cheese effect" and resulting acute toxicity of tranylcypromine arises from its inhibition of MAO-A, which interferes with the metabolism of tyramine. Tyramine is normally metabolized in the gastrointestinal tract by MAO-A. However, when MAO-A is inhibited, tyramine absorption is increased following consumption of tyramine-containing foods such as cheese, beer, herring, etc. This results in the release of catecholamines which can precipitate a hypertensive crisis, producing the "cheese effect." This effect is characterized by Goodman and Gilman as the most serious toxic effect associated with MAO-A inhibitors. Although selegiline is a selective inhibitor of MAO-B at certain dosages and conditions, it produces undesirable inhibition of MAO-A when administered under other conditions, e.g., higher doses. Thus, tyramine sensitivity and the risk of hypertensive crisis increases following oral administration to a human of oral doses of selegiline greater than about 10 mg.

More recently, selegiline has been determined to exhibit direct neuronal effects that may be independent of its MAO-B inhibitory activity. Thus, selegiline is known to be useful for treating diseases and condition associated both with the aforescribed dopaminergic effect and the more recently characterized neuronal protective or regenerative effect.

Because of these significant pharmacological effects, selegiline is known to be useful in a significant variety of diseases and conditions. For example, U.S. patent 4,861,800 (Buyske) discloses the use of selegiline in the treatment of depression, Alzheimer's disease and Parkinson's disease, particularly through the use of transdermal dosage forms, including ointments, creams and patches. U.S. patent 5,242,950 (Hastings) discloses the use of selegiline in the treatment of macular degeneration. U.S. patent 5,151,449 (Milgram) discloses the use of selegiline in the treatment of age-dependent degeneracies, including age-dependent weight loss, the loss of renal function and the loss of cognitive function, including spatial learning ability. U.S. patent 5,276,057 (Milgram and Stevens) discloses the use of selegiline in the treatment of immune system dysfunction. U.S. patent 5,151,419 discloses the use of selegiline in the treatment of schizophrenia. PCT Published Application WO 92/17169 and U.S. patent 5,444,095 disclose the use of selegiline in the treatment of neuromuscular and neurodegenerative disease and in the treatment of CNS injury due to hypoxia, hypoglycemia, ischemic stroke

-3-

or trauma; neurotoxic agents (e.g. MPTP); or amyotrophic lateral sclerosis (ALS).

Selegiline provides neuroprotection or neuronal rescue, by one or more mechanisms, for example, by reducing oxidative neuronal damage, increasing the amount of the enzyme superoxide dismutase, and/or reducing dopamine catabolism. PCT Published Application
5 WO 92/17169 discloses that selegiline acts by directly maintaining, preventing loss of, and/or assisting in, the nerve function of animals.

In addition, selegiline has been disclosed as being useful in the treatment of glaucoma and impotence. See Trope, G. E., et al, "(-)-Deprenyl Improves Visual Function in Glaucoma Patients," Investigative Ophthalmology & Visual Science, 34:2178
10 (March 15, 1994). See also, Knoll, J., et al, "Long-lasting true aphrodisiac effect of (-)-deprenyl in sluggish old male rats," Mod. Problems Pharmacopsychiatry 19:135-153 (1983) and "Sexually low performing male rats die earlier than their high performing peers and selegiline eliminates this difference," Life Sciences 54:1047-1957 (1994).

U.S. patent 5,192,808 (Ruehl) discloses the use of selegiline in the treatment of
15 pituitary-dependent Cushing's disease. For example, in Cushing's disease, the selegiline-like therapeutic effects may be observed in any of a number of common tests used in diagnosing and monitoring the disease (for a discussion of specific tests see, U.S. patent 5,192,808).

Selegiline has also been demonstrated to have clinical efficacy in the treatment
20 attention-deficit, hyperactivity disease (ADHD) and Tourette's Syndrome (TS). See Feigin, A., "A Double-Blind, Placebo-Controlled, Cross-over study of Deprenyl in Children with Tourette's Syndrome (TS) and attention-Deficit Hyperactivity Disorder (ADHD)," Neurology 45 (Suppl. 4):337P (April 1995).

Selegiline is known to be useful when administered to a subject through a wide
25 variety of routes of administration and dosage forms. For example U.S. patent 4,812,481 (Degussa AG) discloses the use of concomitant selegiline-amantadine therapy in which selegiline is used with amantadine in oral, peroral, enteral, pulmonary, rectal, nasal, vaginal, lingual, intravenous, intraarterial, intracardial, intramuscular, intraperitoneal, intracutaneous, and subcutaneous formulations.

30 Buccal and sublingual compositions of selegiline have been described. U.S. patent 5,192,550 (Alza Corporation) describes a dosage form into which selegiline may be incorporated comprising an outer wall with one or more pores in which the wall is

impermeable to deprenyl, but permeable to external fluids. This dosage form is disclosed to be applicable for oral, sublingual or buccal administration. Similarly, U.S. patent 5,387,615 discloses a variety of selegiline compositions, including tablets, pills, capsules, powders, aerosols, suppositories, skin patches, parenterals, and oral liquids, including oil-aqueous suspensions, solutions, and emulsions. Further disclosed therein are selegiline-containing sustained release (long acting) formulations and devices.

Selegiline is metabolized *in vivo* in humans into three main metabolites: desmethylselegiline, amphetamine and methamphetamine. One of the metabolites, desmethylselegiline, does in fact inhibit monoamine oxidase B. However, compared to selegiline, inhibitory activity is exceedingly weak. For example, experiments performed *in vitro* using human platelets have indicated that desmethylselegiline is 68 times less potent than selegiline in inhibiting MAO-B. Similarly, results obtained from mitochondrial-rich fractions from rat cortex and rat brain have indicated that selegiline is approximately 50 times more potent than its desmethyl metabolite as an MAO-B inhibitor and is approximately equal in terms of specificity for MAO-B relative to MAO-A.

The potency of desmethylselegiline as an MAO-B inhibitor *in vivo* has been reported by Heinonen, E. H., *et al.*, ("Desmethylselegiline, a metabolite of selegiline, is an irreversible inhibitor of MAO-B in human subjects," referenced in Academic Dissertation "Selegiline in the Treatment of Parkinson's Disease," from Research Reports from the Department of Neurology, University of Turku, Turku, Finland, No. 33 (1995), pp. 59-61). According to Heinonen, desmethylselegiline appears to have only one-fifth of the MAO-B inhibitory effect of selegiline *in vivo*, *i.e.*, a dose of 10 mg of desmethylselegiline would be required to have the same MAO-B effect as 1.8 mg of selegiline.

The two other principal metabolites of selegiline, amphetamine and methamphetamine, are both known to have neurotoxic effects and are therapeutically undesirable (*see e.g.*, Ryan *et al.*, "Histological and ultrastructural evidence that D-amphetamine causes degeneration in neostriatum and frontal cortex of rats," *Brain Res.* 518:76-77 (1990); Pu *et al.*, "The effects of amfonelic acid, a dopamine uptake inhibitor, on methamphetamine-induced dopaminergic terminal degeneration and astrocytic response in rat striatum," *Brain Res.* 649:217-224 (1994); Ellison, "Continuous amphetamine and

cocaine have similar neurotoxic effects in lateral habenular nucleus and fasciculus retroflexus," *Brain Res.* 598:353-356 (1992)).

The present invention is based upon the discovery that certain diseases and conditions for which selegiline is known to be useful are surprisingly and unexpectedly more advantageously treated by administering selegiline buccally or sublingually rather than by administering selegiline using prior art methods, e.g., oral administration. Accordingly, the novel methods disclosed herein produce enhanced therapeutic effects.

Summary of the Invention

The present invention particularly includes:

an improved method for obtaining a selegiline-like therapeutic effect in a mammal suffering from (a) a neuronal-degenerative, selegiline-responsive disease or condition, (b) depression, or (c) attention-deficit, hyperactivity disease (ADHD), comprising:

administering selegiline, or a pharmaceutically acceptable salt thereof, to said mammal in a buccal or sublingual dosage form, wherein said selegiline, or pharmaceutically acceptable salt thereof, is administered in an amount sufficient to produce a selegiline-like therapeutic effect.

The present method is employed in any neuronal-degenerative condition or disease in which selegiline produces a beneficial therapeutic effect. For the purposes of the present invention, the term "neuronal-degenerative" refers to those diseases or conditions where the effect of selegiline is not associated with any known dopaminergic effects. Thus, for example, the term excludes reference to diseases like Parkinson's Disease, depression, and attention-deficit, hyperactivity disease in which dopaminergic activity is reported to be implicated in the therapeutic action of selegiline.

However, the term "neuronal-degenerative" does refer to selegiline-responsive diseases and conditions leading to, or caused by, neuronal degeneration in which selegiline has a favorable effect on the survival of the neurons implicated in the disease condition. Included among these are those directly associated with neuronal damage, for example, injury due to hypoxia, ischemia, stroke; trauma (e.g., damage due to mechanical injury), and chemotoxic damage. Moreover, neuronal-degenerative diseases and conditions encompass those conditions in which neuronal dysfunction or death is part of a more complex etiologic process, for example, Alzheimer's disease and other neurodegenerative dementias, multiple sclerosis, and amyotrophic lateral sclerosis (ALS).

-6-

In either event, the typical selegiline-like therapeutic effects would include a reduction in the number of neurons damaged or lost; increased neuronal regrowth; improved cognitive and physical capabilities; and improved memory (see U.S. patent 5,444,095; U.S. patent 5,225,446; and PCT application WO 92/17169).

5 Finally, the neuronal degenerative processes included within the ambit of the present method include those where neuronal loss is attributable to the aging process or other pathologies. Among these neuronal-degenerative conditions are weight loss; diabetic and related neuropathies, loss of renal function and immune system dysfunction. Typical selegiline-like therapeutic effects would include reduced weight loss; reduced
10 blood urea nitrogen levels; reduction in the age related proliferation of peripheral blood lymphocytes; maintenance of a higher CD4/CD8 ratio; and increased blood levels of antigen-specific immunoglobulins after antigen challenge (see U.S. patents 5,151,449; 5,276,057 and 5,387,615).

15 Glaucoma and macular degeneration represent two visual conditions that have been reported as being amenable to selegiline treatment in accordance with the present method. In particular, selegiline is thought to improve the visual acuity of animals with these conditions. The present method, in which selegiline is delivered buccally or sublingually, represents an improvement in this treatment (see U.S. patent 5,242,950).

20 The present method may also be applied to certain selegiline-responsive diseases and conditions where the dopaminergic activity of selegiline is known to produce a useful therapeutic response. These selegiline-response diseases are referred to herein as "dopaminergic-related, selegiline-responsive diseases or conditions." The dopaminergic-related, selegiline responsive diseases or conditions of the present invention are:
25 attention-deficit, hyperactivity disease (ADHD) and Tourette's syndrome, depression, post-polio syndrome, narcolepsy, chronic fatigue syndrome, schizophrenia, tardive dyskinesia, alopecia, and the treatment of pituitary-dependent Cushing's disease.

30 The total daily dosage of selegiline administered to an animal or patient, typically a human patient, should be at least the amount required to induce a selegiline-like therapeutic effect. The term "selegiline-like therapeutic effect" refers to one of the known therapeutic or prophylactic effects of selegiline in an animal or patient. Typical therapeutic effects would include: an increase in neuronal survival after trauma or in response to a neurodegenerative disease; reduced loss of cognitive or physical

capabilities; reduced loss of memory; retardation of age dependent weight loss or immune system dysfunction; improved renal function; and reduced loss of vision.

The actual dosage required to effect such a result is influenced by a number of clinical factors, but will preferably require at least about 0.0015 mg per kg of body weight of selegiline per day and, more preferably, between about 0.01 and 0.15 mg/kg per day. Dosage is calculated on the basis of the free secondary amine form of selegiline and may be provided in either a single or multiple dosage regimen. The optimal daily dose of selegiline useful for the purposes of the present invention is determined by methods known in the art and will be influenced by factors such as the condition or disease being treated, the severity of the condition or disease, the condition of the subject to whom treatment is being given, the desired degree of therapeutic response, and the concomitant therapies being administered to the patient or animal. Ordinarily, the attending physician or veterinarian will administer an initial daily dose of at least about 0.01 mg per kg of body weight, calculated on the basis of the free secondary amine, with progressively higher doses being employed depending upon the response to the therapy. Typically, the daily dose will be about 0.01 mg/kg of body weight and may extend to about 0.15 mg/kg of body weight (all such doses again being calculated on the basis of the free secondary amine). These are simply guidelines since the actual dose must be carefully selected and titrated by the attending physician or veterinarian depending upon the age, weight, clinical condition and observed response of the individual patient or animal.

The daily dose can be administered in a single or multiple dosage regimen.

Buccal and sublingual dosage forms of selegiline are prepared utilizing known techniques, e.g., the techniques described for example in U.S. patent 5,192,550; U.S. patent 5,221,536; U.S. patent 5,266,332; U.S. patent 5,057,321; U.S. patent 5,446,070; U.S. patent 4,826,875; U.S. patent 5,304,379; or U.S. patent 5,354,885.

Buccal or sublingual formulations for use in the present methods may employ selegiline either in the form of a free base or as a pharmaceutically acceptable acid addition salt. In the latter case, the hydrochloride salt is generally preferred. However, other salts useful in the present invention include those derived from organic and inorganic acids such as, without limitation, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulphonic acid, acetic acid, tartaric acid, lactic acid, succinic acid, citric

acid, malic acid, maleic acid, aconitic acid, salicylic acid, phthalic acid, embonic acid, enanthic acid, and the like.

The methods disclosed herein may be used for both human and non-human subjects. With regard to the latter, the methods are particularly, but not exclusively, directed to domesticated mammals such as canine and feline species.

Detailed Description of the Invention

Example 1: Buccal Selegiline Tablet

A buccal tablet is formulated from the following ingredients:

	Ingredient	Weight (mg/unit dose)
10	Selegiline HCl	5.00
	Hydroxypropylmethycellulose (HPMC)	5.00
	Lactose	186.00
	Citric Acid (anhydrous)	2.00
	Magnesium stearate	2.00

15 Prepare a granulate from the first four ingredients by first passing ingredients 1, 3 and 4 through a 25-mesh hand screen and thereafter blend. Prepare a 10% solution of HPMC in water (10 g HPMC per 100 g of solution) and granulate this solution into the dry ingredients. Pass the wet mass through a #10 screen and spread onto a paper-lined tray, drying for three hours at 130° C. Blend the resulting granulate with ingredient 5
20 and compress into a tablets.

Example 2: Sublingual Selegiline Tablet (Non-Effervescent)

A sublingual tablet is prepared from the following ingredients:

	Ingredient	Weight (mg/unit dose)
	Selegiline HCl	5.00
25	Croacarmellose sodium	5.00
	Lactose	186.00
	Citric Acid (anhydrous)	2.00
	Magnesium stearate	2.00

30 Pass the first three ingredients above through a 25-mesh hand screen and blend and mix for seven minutes. After passing ingredient 4 above through a #60 hand mesh,

add to the mix with the remaining blended ingredients and blend for an additional 3 minutes. Compress the resulting mixture into tablets.

Example 3: Sublingual Selegiline Tablet (Effervescent)

A sublingual tablet is prepared from the following ingredients:

5	Ingredient	Weight (mg/unit dose)
	Selegiline HCl	5.00
	Citric Acid (anhydrous)	100.00
	Sodium bicarbonate	185.00
	Fumaric acid	10.00

10 The compositions, prepared above, or known buccal or sublingual compositions, or buccal or sublingual compositions prepared using known methods are then employed in the methods described above.

CLAIMS

1. An improved method for obtaining a selegiline-like therapeutic effect in a mammal suffering from (a) a neuronal-degenerative, selegiline-responsive disease or condition, (b) depression, or (c) attention-deficit, hyperactivity disease (ADHD), comprising:
 - 5 administering selegiline, or a pharmaceutically acceptable salt thereof, to said mammal in a buccal or sublingual dosage form, wherein said selegiline, or pharmaceutically acceptable salt thereof, is administered in an amount sufficient to produce a selegiline-like therapeutic effect.
2. A method of claim 1, wherein selegiline is administered as the free base.
- 10 3. A method of claim 1, wherein said selegiline is administered as a pharmaceutically acceptable acid addition salt.
4. A method of claim 3, wherein said pharmaceutically acceptable acid addition salt is the hydrochloride salt.
5. A method of claim 4, wherein said mammal is a human.
- 15 6. A method of claim 5, wherein said disease or condition is a consequence of hypoxia, ischemia, or stroke.
7. A method of claim 5, wherein said neuronal degeneration is due to trauma.
8. A method of claim 5, wherein said disease or condition is Alzheimer's disease.
9. A method of claim 5, wherein said disease or condition is ALS.
- 20 10. A method of claim 5, wherein said disease or condition is age dependent weight loss.
11. A method of claim 5, wherein said disease or condition is characterized by immune system dysfunction.
12. A method of claim 5, wherein said disease or condition is Cushing's disease.
13. A method of claim 5, wherein said disease or condition is glaucoma.
- 25 14. A method of claim 5, wherein said disease or condition is macular degeneration.
15. A method of claim 5, wherein said disease or condition is attention deficit, hyperactivity disease (ADHD).
16. A method of claim 5, wherein said disease or condition is depression.
17. A method of claim 5, wherein said disease or condition is a loss of renal function.
- 30 18. A method according to any of the preceding claims wherein the dose of selegiline is greater than about 0.01 mg/kg/day.

-11-

19. A method according to any of the preceding claims wherein the administration is buccal.
20. A method according to any of the preceding claims wherein the administration is sublingual.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/17745

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/135

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 96 26720 A (SCHERER LTD) 6 September 1996 see the whole document ---	1-20
A	US 4 861 800 A (BUYSKE) 29 August 1989 cited in the application ---	
A	US 5 242 950 A (FRIES HASTINGS) 7 September 1993 cited in the application ---	
A	US 5 151 449 A (MILGRAM) 29 September 1992 cited in the application ---	
A	US 5 276 057 A (MILGRAM ET AL.) 4 January 1994 cited in the application ---	
	-/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

& document member of the same patent family

Date of the actual completion of the international search

27 February 1997

Date of mailing of the international search report

14.03.97

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+ 31-70) 340-3016

Authorized officer

Klaver, T

INTERNATIONAL SEARCH REPORT

International Application No

PCI/US 96/17745

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 444 095 A (TATTON ET AL.) 22 August 1995. cited in the application -----	

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/US 96/17745

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9626720 A	06-09-96	AU 4884696 A	18-09-96
US 4861800 A	29-08-89	CA 1329132 A	03-05-94
		AU 628340 B	17-09-92
		AU 3502289 A	22-11-90
		CN 1048320 A	09-01-91
		EP 0406488 A	09-01-91
		US 4868218 A	19-09-89
		US RE34579 E	05-04-94
US 5242950 A	07-09-93	AU 4033993 A	29-11-93
		CA 2133998 A	11-11-93
		EP 0637238 A	08-02-95
		HU 72295 A	29-04-96
		JP 7505906 T	29-06-95
		NO 944018 A	21-10-94
		WO 9321894 A	11-11-93
US 5151449 A	29-09-92	AU 633714 B	04-02-93
		AU 7395791 A	05-03-92
		CA 2039194 A,C	01-03-92
		EP 0473252 A	04-03-92
		EP 0732101 A	18-09-96
		JP 4230624 A	19-08-92
		US 5387615 A	07-02-95
		US 5565495 A	15-10-96
		US 5561163 A	01-10-96
		US 5192808 A	09-03-93
		US 5225446 A	06-07-93
		US 5276057 A	04-01-94
US 5276057 A	04-01-94	US 5151449 A	29-09-92
		US 5387615 A	07-02-95
		US 5565495 A	15-10-96
		US 5561163 A	01-10-96
		AU 633714 B	04-02-93
		AU 7395791 A	05-03-92
		CA 2039194 A,C	01-03-92
		EP 0473252 A	04-03-92
		EP 0732101 A	18-09-96

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 96/17745

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5276057 A		JP 4230624 A	19-08-92
		US 5192808 A	09-03-93
		US 5225446 A	06-07-93

US 5444095 A	22-08-95	AU 1450592 A	02-11-92
		WO 9217169 A	15-10-92
		EP 0578687 A	19-01-94
		JP 6506204 T	14-07-94
